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NOVEL APPLICATIONS OF MCE (MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY) IN CORONARY ARTERY DISEASES WITH DIFFERENT SITUATIONS

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ABSTRACT

Myocardial contrast echocardiography (MCE)can be a feasible alternative to the widely used radionuclide single-photon emission computed tomography (SPECT), which is often limited by higher costs, exposure to radiation, poor spatial resolution and frequent attenuation artefacts.MCE is useful to detect coronary artery disease on basis of myocardial perfusion. Many studies have demonstrated concordance between MCE and SPECT for assessment of Myocardial Perfusion during rest and stress. Myocardial contrast echocardiography also provides higher sensitivity as well as incremental prognostic value over and above Wall Motion in patients with stable coronary artery diseases (CAD). Importantly, the higher sensitivity of MCE over Wall Motion is independent of the type of stress modality used.

1. Introduction:

Myocardial contrast echocardiography (MCE) is an imaging tool for the assessment of the myocardial microcirculation. It utilizes gas-filled microbubbles that are inert, remain entirely within the vascular space, and possess an intravascular rheology similar to that of red blood cells. During an intravenous infusion of these microbubbles and attainment of a steady state, the microbubbles are destroyed with high energy ultrasound and the rate of microbubble replenishment within the ultrasound beam is measured (Figure 1), which represents mean red blood cell velocity.

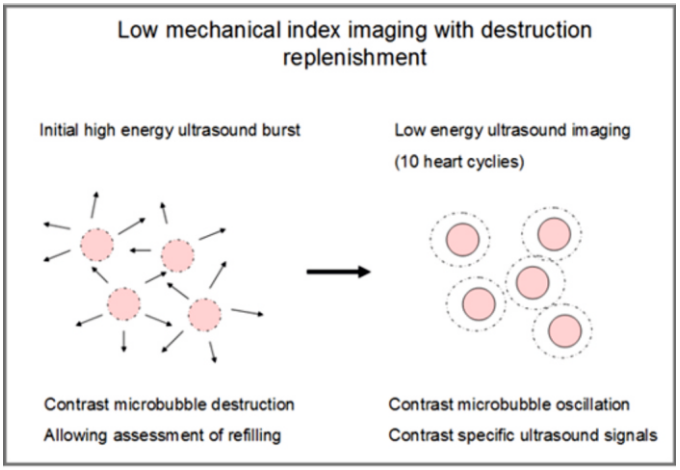

Figure-1 Microbubble replenishment

Normally, the beam fills within 5 seconds when resting flow is normal. It takes longer to fill when flow is reduced and fills faster at hyperemic flows. When the beam is fully replenished, the ultrasound signal represents relative blood volume within the beam, which translates to the volume of blood within the myocardium itself. Normalizing this value to the signal from the left ventricular cavity provides a measure of blood volume fraction. Therefore, unlike other experimental and clinical methods that measure myocardial blood flow (MBF), this approach provides an assessment of the 2 individual components of nutrient tissue (capillary) perfusion: Blood volume fraction and flow velocity. The product of the two is proportional to MBF. Other than the heart, this method has been used successfully and accurately for the measurement of tissue perfusion in the skeletal muscle,skin,brain, and kidney.In this update, we shall review the clinical use of this technique in 4 clinical settings: and detection of coronary artery disease (CAD), Acute myocardial infarction (AMI) , Restenosis after revascularization, Non-obstructive coronary artery disease .

2. Detection of Coronary Artery Disease:

If there is no prior AMI, detection of CAD requires some form of stress testing. For MCE, we prefer a coronary vasodilator, although dobutamine is also sometimes used. The advantage of a vasodilator is shorter examination time, fewer side effects, and easier image interpretation because of absence of tachycardia and tachypnea-induced cardiac motion. It is currently not possible to perform MCE in patients exercising on the treadmill. For interpretation, end-systolic images acquired at rest and stress are placed side-by-side. In this manner, we can compare the same region within the stress and rest images at the same pulsing interval. Unlike nuclear cardiology, we do not compare different regions within the same image.

As stated earlier, the ultrasound beam should replenish in 5 seconds at rest if the resting flow is normal. If maximal hyperemia (5 times normal flow) is achieved with a vasodilator, then the stress image should fill in 1 second. Thus, the 5-second rest image should look exactly like the 1-second stress image. A lack of this finding suggests reduced coronary blood flow reserve. If this finding is regional, it indicates the presence of CAD. When this finding is global, it usually indicates reduced flow reserve due to other systemic conditions, such as hypertension, diabetes, or hyperlipidemia.

When we perform vasodilator stress, we prefer intermittent high mechanical index imaging. During dobutamine stress, however, we prefer low mechanical index imaging in order to simultaneously examine regional function, shown in the case discussed below. In addition to the rapid filling seen with dobutamine, we also see an appreciable increase in myocardial opacification because dobutamine increases myocardial blood volume. At low doses, dobutamine is a vasodilator, and at higher doses it recruits more capillaries to meet the increased myocardial oxygen needs. Lack of increase in myocardial opacification also indicates the presence of CAD. Similar to vasodilators, dobutamine can cause a decrease in myocardial blood volume distal to a stenosis, resulting in a perfusion defect. The decrease of blood volume occurs from capillary de-recruitment in an attempt to maintain a constant capillary hydrostatic pressure in the face of a decrease in perfusion pressure caused by hyperemia.

An 65-year-old man was referred for dobutamine stress echocardiography because of atypical chest pain. She had left ventricular hypertrophy with generalized repolarization changes on the ECG. She underwent both regional perfusion and regional function assessment using a constant infusion of Definity during low mechanical index, real-time MCE that allows simultaneous assessment of regional perfusion and function (at 20 Hz instead of the usual 30 Hz). The patient demonstrated no perfusion defect at rest (Figure 2 A), but developed a defect at a dose of 20 μg . $kg^{-1} \cdot min^{-1}$ at a time when wall motion was still normal (Figure 2B). At a dobutamine dose of 40 μg · $kg^{-1} \cdot min^{-1}$, both perfusion and function became abnormal (Figure 2C). Note that the normal region shows increased myocardial opacification compared with baseline and lower dobutamine dose. Coronary angiography revealed a proximal left circumflex artery stenosis and a dominant left coronary system

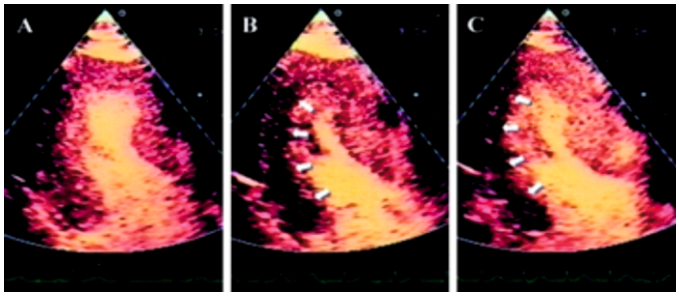

Figure 2. A-no perfusion defect at rest, B- wall motion was still normal, C-both perfusion and function became abnormal.

Because of the ischemic cascade, perfusion abnormalities precede wall motion abnormalities as shown above and therefore have a higher sensitivity both for the detection of CAD, as well as for identification of multivessel disease.

3. ST elevetion of myocardial infarction (STEMI)

In acute STEMI the recommended treatment is immediate coronary angiography and revascularization. Contrast echocardiography can assess area at risk and help in diagnosing acute myocardial infarction in patients with acute chest pain and a non-diagnostic ECG, particularly common in patients with acute occlusion of the circumflex artery . But contrast echocardiography will not be indicated in pre-catheterization evaluation of most patients with STEMI.(See Figure-3.)

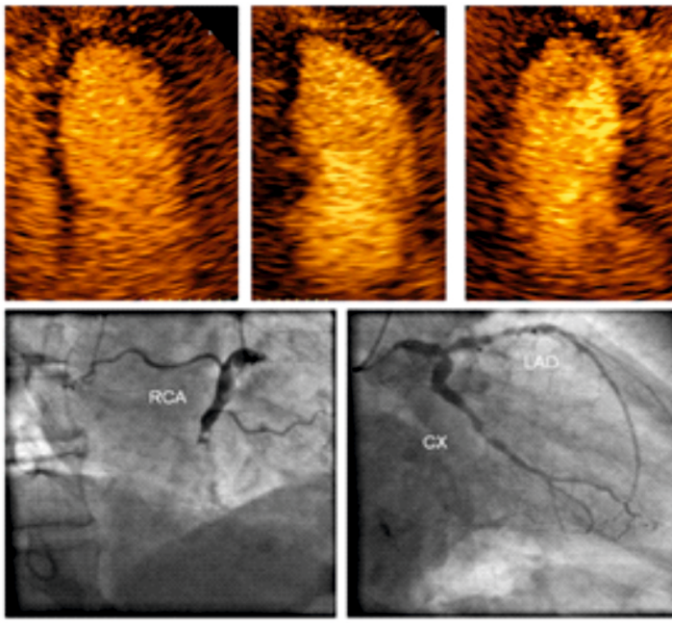

Figure-3.-Contrast echocardiography in apical 4-chamber, 2-chamber and 3-chamber views (upper panels) demonstrating the extensive reduction of myocardial perfusion in a NSTEMI patient with angiographic trippel-vessel disease including acute occlusion of the right coronary artery and left main stem stenosis (lower panels).

In spite of successful reopening of the infarct related artery by percutaneous coronary intervention, some STEMI patients still develop unexpectedly large myocardial infarctions due to the no-reflow phenomenon. The no-reflow phenomenon is caused by impaired microcirculation which can be a consequence of peripheral embolization during the percutaneous revascularization procedure or revascularisation damage due to inflammation and oedema causing microvascular obstruction and subsequent myocardial necrosis. The no-reflow phenomenon after revascularization can be diagnosed by MCE . Lack of reperfusion after coronary intervention predicts myocardial necrosis, reduced left ventricular function, left ventricular remodelling and subsequent development of heart failure. Thus, MCE may be used in STEMI patients to identify successful reopening of the infarct related artery and to give prognostic information by identifying patients with no-reflow who need additional treatment in the acute and chronic phase of a STEMI .

In addition to guide and evaluate treatment, an ongoing study evaluates the effect of ultrasound contrast enhanced thrombolysis in acute treatment of STEMI. The ongoing Sonolysis trial uses a combination of ultrasound induced contrast microbubbles destruction at high mechanical index ultrasound and thrombolysis, where destruction of microbubbles causes streaming and thereby improves the effect of thrombolysis in reopening of the infarct related artery .

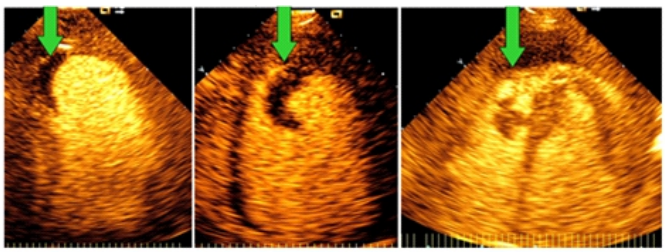

Figure-3. Complications in acute myocardial infarction. Myocardial mural thrombus in the apex of the left ventricle, with lack of contrast enhancement due to the thrombus avascular characteristics (Panel A and B). In comparison, the typical contrast enhancement in a patient with pulmonary carcinoma and a myocardial metastasis in the right ventricle (Panel C).

Development of intraventricular mural thrombus is a feared complication to acute myocardial infarction which untreated may lead to severe thromboembolic episodes. A magnetic resonance study demonstrated that mural thrombus formation in patients with acute coronary syndromes may be more common than previously anticipated . However, suspected mural thrombus may be ruled out in about 90% of patients by contrast echocardiography .Diagnosing a mural thrombus with contrast echocardiography is simple and can be performed with a single ultrasound contrast bolus injection. A mural thrombus is characterized by a lack of contrast enhancement due to its avascular nature (Fig 3 Panel A and B). In contrast, a myocardial tumor is characterized by contrast enhancement which is particular high in malignant tumores that are highly vascularised structures (Fig.3 panel C).

In acute myocardial infarction, myocardial rupture is a rare and deadly complication. A rupture of the free ventricular wall is usually associated with sudden death, but occasionally, epicardial coverage occurs and subsequent formation of a ventricular pseudoaneurysm. Ventricular pseudoaneurysms can be difficult to diagnose by conventional echocardiography (Fig. 4 left panel), but are easy to recognize after injection of an ultrasound contrast agent during imaging (Fig. 4 right panel).

4. Restenosis after revascularization .

In patients undergoing percutaneous coronary intervention with stent implantation, 10-30% will develop significant angiographic restenosis in spite of initial successful treatment. Restenosis is caused by intimal hyperplasia and is asymptomatic in 50% of patients .However, even in asymptomatic patients development of restenosis is associated with a poorer prognosis .

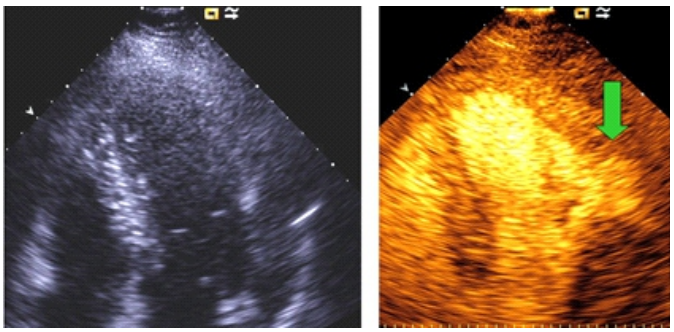

Figure-4. Extracardial contrast enhancement due to a pseudoaneurysm in the lateral wall of the left ventricle (right panel) not visible with conventional echocardiography (left panel).

Non-invasive diagnosis of restenosis can be challenging. Previous SPECT studies have demonstrated that normalization of regional myocardial perfusion usually occurs after successful revascularization . In a follow-up study using quantitative contrast stress echocardiography in 33 patients with stable angina pectoris treated with percutaneous coronary intervention and stent implantation, there was no improvement in stress-induced myocardial perfusion during follow-up in patients who had developed a significant angiographic restenosis, while the stress-induced perfusion was improved in patients with successful revascularisation at 9 months .

At present, quantitative contrast stress echocardiography is not recommended in routine assessment of coronary artery disease due to inter-individual variation and lack of data on normal values and cut-off values indicating ischemia for this method. Still, serial assessment in individual patients may be useful.

5. Non-obstructive coronary artery disease .

Although coronary angiography remains the gold standard for diagnosis of coronary artery disease, it should be kept in mind that myocardial ischemia may be present in spite of angiographically open epicardial coronary arteries, a condition known as non-obstructive ischemic heart disease. This condition cannot be diagnosed using angiography alone, but requires additional use of perfusion assessment with cardiac magnetic resonance or MCE. In patients with acute coronary syndrome, non-obstructive ischemic heart disease is present in 15% of women and 9% of men . Cardiac magnetic resonance studies in NSTEMI patients have demonstrated myocardial infarction in up to 34% of patients with normal coronary arteries by coronary angiography. Clot autolysis and recanalisation of the infarct related artery are the main reasons for this finding as well as microvascular disease that can not be detected by coronary angiography, the current diagnostic gold standard. In patients with recurrent hospitalisation for chest pain and “normal” coronary arteries by coronary angiography additional non-invasive cardiac imaging should be performed. MCE can be used to diagnose myocardial ischemia in such patients and thereby distinguish between patients with non-cardiac chest pain and patients with non-obstructive ischemic heart disease. Non-obstructive ischemic heart disease most often is caused by microvascular disease associated with diabetes mellitus, obesity and hypertension, but also hemodynamic changes like increased left ventricular filling pressure and increased arterial stiffness can cause reduced myocardial perfusion pressure and hence myocardial ischemia despite angiographically normal epicardial coronary arteries . Chronic myocardial ischemia in such patients may promote development of myocardial fibrosis and secondary structural changes in the left ventricle, finally leading to functional impairment and heart failure .

Another recently recognized condition mainly affecting women is the Takotsubo

cardiomyopathy, mimicking an acute myocardial infarction. The exact pathophysiological mechanism remains unknown in Takotsubo cardiomyopathy, but it involves myocardial hypoperfusion that can be diagnosed by contrast echocardiography causing functional impairment mainly in the apical part of the left ventricle with the characteristic apical ballooning (Fig. 5) . The microvascular involvement is also confirmed by early cardiac MRI demonstrating late gadolinium uptake suggesting diffuse microcirculation damage .Contrast echocardiography in apical 4-chamber, 2-chamber and 3-chamber views (upper panels) demonstrating the extensive reduction of myocardial perfusion in a NSTEMI patient with angiographic trippel-vessel disease including acute occlusion of the right coronary artery and left main stem stenosis (lower panels).

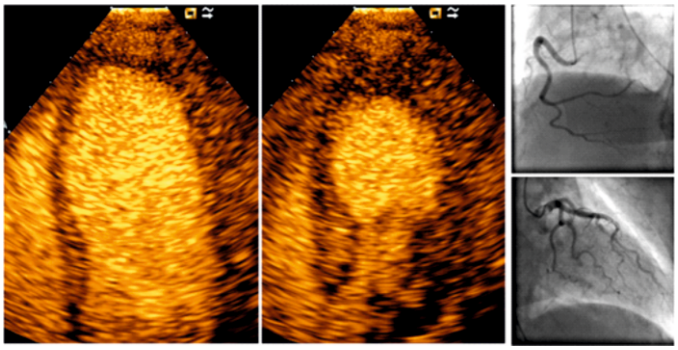

Figure-5 Takotsubo Cardiomyopathy. Contrast echocardiography in diastole and systole illustrating the apical akinesia and ballooning of the left ventricle in an apical 4-chamber view, in addition there is a delayed contrast enhancement in the apical segments of the left ventricle. The right panel shows the normal coronary angiogram confirming the diagnosis Takotsubo cardiomyopathy.

Conclusions:

MCE is a rapid bedside method for assessing myocardial perfusion both at rest and stress. It has been performed safely in several thousand patients. As of yet there is no ultrasound contrast agent that has been approved for MCE by the US Food and Drug Administration. Most of the clinical experience gained has been in the research setting. Once ultrasound contrast agents are approved for MCE and reimbursement is determined, this modality should experience increased use in clinical cardiology.

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